REMARKS

I. Claim Status

Claims 1-37 were originally filed and were subject to restriction. In the Office Action dated 22 February 2007, the Examiner rejoined the claims of Group I and Group II, claims 1-37.

Claims 38-48 were previously presented in the Amendment dated 19 December 2008. Claims 49-56 were previously presented in the Amendment dated 26 May 2009. Claims 1-42 were previously canceled. Accordingly, claims 43-56 are currently under examination.

II. Rejection of claims 43-56 under 35 U.S.C. §112, 1st paragraph

The Examiner rejected claims 43-56 under 35 U.S.C. §112, 1st paragraph, for lack of enablement. In particular, the Examiner stated that "while being enabling for a method for treating diabetes in a diabetic subject, the method comprising administering to the subject an effective amount of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase, wherein the compound [is] selected from the group consisting of [eight exemplified compounds]...does not reasonably provide enablement for a method for treating diabetes...comprising administering...an effective amount of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase...." (See Office Action, page 2.) Applicants respectfully traverse this rejection.

The Examiner bears the burden of providing an explanation as to why the claims are not adequately enabled by the specification. *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993). In the final office action mailed 23 September 2009, the Examiner stated that "it is apparent that there is undue experimentation because of a variability in prediction of outcome that is not addressed by the present application. Absent factual data to the contrary, the amount and level of experimentation needed is undue to practice the invention as claimed." (Office Action, pages 4 and 5.) The Examiner further reasoned that "others skilled in the art would be unable to practice the invention as claimed without undue experimentation and with[out] a reasonable expectation of success, other than the use of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase, wherein the compound [is] selected from the group consisting of [eight exemplified compounds]." (Office Action, page 5.) Applicants respectfully submit that the Examiner has failed to meet his burden of establishing a factual basis to support a

conclusion that the use of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase would not be effective for treating diabetes, treating hyperglycemia, and reducing blood glucose levels in a subject. Specifically, the Examiner has provided no evidence demonstrating the unpredictability of heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase in treating diabetes, treating hyperglycemia, and reducing blood glucose levels. The Examiner's mere assertion to that effect is not sufficient for establishing a *prima facie* case of lack of enablement.

Instead, based on the specification and the evidence of record, those of skill in the art would expect similar results by following the teachings of the instant specification to inhibit HIF hydroxylase activity using heterocyclic carbonyl glycine compounds available in the art as of the filing date. In particular, the examples provided in the specification show effective use of eight different heterocyclic carbonyl glycine compounds representing four distinct chemical classes in the treatment of diabetes and hyperglycemia and in the reduction of blood glucose levels in a subject. The Examiner has not shown any evidence that HIF hydroxylase inhibition with other known heterocyclic carbonyl glycine compounds would require trial and error experimentation to achieve the degree of therapeutically effective results reported in the present application. The present inventors were the first to show that inhibition of HIF hydroxylase activity using known heterocyclic carbonyl glycine compounds was effective at treating diabetes, treating hyperglycemia, and reducing blood glucose levels *in vivo*.

The Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention and no such evidence or scientific reasoning is present in the instant rejection. See *In re Wright*, 999 F.2d 1557, 1561-62 (Fed. Cir. 1993) (Examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). The Examiner has not shown any HIF hydroxylase specific evidence that would lead one of skill to expect results differing from those achieved in the instant application by the use of other heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase. Since the Examiner has not provided the required evidence or scientific reasoning to show that one of ordinary skill in the art would find that treating diabetes in a diabetic subject with a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase would have required "undue experimentation," the rejection of claims 43-56 under 35 U.S.C. §112 for lack of enablement must be withdrawn.

Moreover, the Examiner's apparent assertion that, in order to show enablement, the specification must provide "factual data" showing that "the amount and level of experimentation needed is [not] undue" is contrary to controlling case law. Applicants must "teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997). There is no burden on Applicants to show "factual data" of the absence of undue experimentation.

Even assuming, *arguendo*, that the Examiner could establish a *prima facie* case of lack of enablement; the claimed methods are clearly enabled under a proper *Wands* analysis. "[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997)(quoting *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993)). "[T]he question of undue experimentation is a matter of degree. The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.'" *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). "Factors to be considered in determining whether a disclosure would require undue experimentation . . . . include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). "It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. However, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed." *In re Vaeck*, 947 F.2d 488, 496 & n. 23 (Fed.Cir.1991).

Each *Wands* factor is addressed below on the basis of the specification, the claims, and the Examiner's factual findings.

Nature of the Invention and Breadth of the Claims

Independent claim 43 encompasses a method for "treating diabetes in a diabetic subject, the method comprising administering to the subject an effective amount of a heterocyclic carbonyl glycine compound which inhibits a hypoxia inducible factor (HIF) hydroxylase, thereby treating diabetes in the subject." Thus, use of compounds having the required structural limitation, i.e., heterocyclic carbonyl glycine compounds, and specific functional limitation, inhibit a hypoxia inducible factor (HIF) hydroxylase, for treating diabetes in a diabetic subject are encompassed by the claim.

Quantity of Experimentation

The Examiner made no factual findings regarding the quantity of experimentation. Applicants submit that there is no evidence showing that a large quantity of experimentation would be required to recognize that a claimed compound (having the structure and activity recited in the claims) could effectively treat diabetes. The Examiner only asserts that "the amount and level of experimentation needed is undue to practice the invention as claimed." (Office Action, page 5.) Contrary to the Examiner's assertion, the specification teaches both *in vitro* and *in vivo* assays showing the therapeutic effects of heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase in treating diabetes. Indeed, all of the exemplified heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase listed in the specification were effective for use in treating diabetes in these assays.

Skill in the Art

The Examiner made no factual findings regarding the skill in the art.

Amount of Direction or Guidance Presented

The Examiner stated that "Applicant[s] have provided no guidance of any other ingredient which acts as a heterocyclic carbonyl glycine which inhibits HIF hydroxylase." (Office Action, page 4.) On the contrary, the specification teaches that "small molecule inhibitors of HIF hydroxylases have also been identified. (See, e.g., International Publication Nos. WO 02/074981, WO 03/049686, and WO 03/080566, all incorporated herein by reference in their entirety.) The present invention specifically contemplates the use of these [compounds]." (Specification, paragraph [0134].) The specification also teaches that exemplary compounds that "inhibit HIF hydroxylase" include "heterocyclic carbonyl glycines including, but not limited to, substituted quinoline-2-carboxamides and esters thereof as described, e.g., in U.S. Patent Nos. 5,719,164 and 5,726,305; substituted isoquinoline-3-carboxamides and esters thereof as described, e.g., in U.S. Patent No. 6,093,730; 3-methoxy pyridine carbonyl glycines and esters thereof as

described, e.g., in European Patent No. EP 0 650 961 and U.S. Patent No. 5,658,933; 3 hydroxypyridine carbonyl glycines and esters thereof as described, e.g., in U.S. Patent Nos. 5,620,995 and 6,020,350." (Specification, paragraph [0137].) These U.S. and European patents demonstrate that HIF hydroxylase inhibitors were available in the art at the time of filing. The instant specification also teaches assays and methods for identifying other heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase for use in the claimed methods. (See, e.g., Specification, paragraphs [0140]-[0145].) Further, the specification provides evidence showing eight exemplary heterocyclic carbonyl glycine compounds representing four distinct classes of HIF hydroxylase inhibitors were effective at treating diabetes, treating hyperglycemia, and reducing blood glucose levels. (Specification, paragraph [0139].) Thus, contrary to the Examiner's assertion, the specification provides guidance to one of skill for other heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase for use in the claimed methods.

Presence of Working Examples

The Examiner stated that the specification is "enabling for a method for treating diabetes in a diabetic subject, the method comprising administering to the subject an effective amount of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase." (Office Action, page 2.) The specification teaches that administration of heterocyclic carbonyl glycine compounds to mice "specifically induce[d] direct mediators of blood glucose uptake and indirect effects on hormonal regulators of blood glucose and glucose regulation." (Specification, paragraph [0167].) The specification also teaches that heterocyclic carbonyl glycine compounds administered *in vitro* "are useful for increasing expression of proteins involved in glucose uptake, and thus provide a therapeutic approach to enhance glucose uptake and lower blood glucose levels, particularly in patients with hyperglycemia, diabetes." (Specification, paragraph [0157].) The specification further teaches that "animals treated with compound of the invention showed a dose-dependent decrease in blood glucose levels" and thus "methods and compounds of the invention are useful to therapeutically decrease blood glucose levels in a subject." (Specification, paragraph [0173].) The specification also teaches that in an animal model of Type 2 diabetes, administration of heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase "improved glucose clearance from blood, decreased blood glucose levels, normalized glucose tolerance, and restored glucose homeostasis." (Specification, paragraph [0176].) The specification further teaches that treatment of animals with heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase "reduced the accumulation of glycated hemoglobin in a model of Type 2 diabetes" and therefore "indicate[d] that such compounds of the invention are useful to therapeutically improve glycemic control in patients with diabetes or hyperglycemia." (Specification, paragraph [0181].) Clearly, the specification provides

substantial working examples regarding methods of administering heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase to treat diabetes, to treat hyperglycemia, and to reduce blood glucose levels in subjects.

State of the Art and Predictability of the Art

The specification teaches that heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase were known in the art at the time of filing. (See, e.g., Specification, paragraph [0137].) For example, the specification teaches that "small molecule inhibitors of HIF hydroxylases have also been identified. (See, e.g., International Publication Nos. WO 02/074981, WO 03/049686, and WO 03/080566, all incorporated herein by reference in their entirety.) The present invention specifically contemplates the use of these and other compounds that can be identified using methods known in the art." (Specification, paragraph [0134].) These published patent applications indicate that other HIF hydroxylase inhibitors were available to one of skill in the art at the time of filing. For example, International Publication No. WO 03/049686 discloses that HIF hydroxylase inhibitors have been identified and are available.

The Examiner made no factual findings regarding the predictability of the art. Specifically, the Examiner has provided no evidence demonstrating the unpredictability of heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase in treating diabetes. Applicants submit that the art recognized heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase and that all of the exemplified heterocyclic carbonyl glycines that inhibit HIF hydroxylase listed in the specification were effective for use in treating diabetes.

In analyzing the *Wands* factors, based upon the specification and the evidence presented by the Examiner, all of the factors are neutral or weigh in favor of Applicants and clearly show that undue experimentation would not be required to make and use the claimed invention. Even the factor of "the predictability or unpredictability of the art" weighs in favor of Applicants, since the Examiner made no factual findings that treatment of diabetes, treatment of hyperglycemia, or reduction of blood glucose levels with heterocyclic carbonyl glycine compounds meeting the functional requirements of claims 43-56 would be unpredictable. The specification provides *in vitro* and *in vivo* working examples showing the therapeutic effects of heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase in treating diabetes, treating hyperglycemia, and reducing blood glucose levels. The specification also provides guidance to one of skill in the art for other heterocyclic carbonyl glycine compounds that inhibit HIF hydroxylase for use in the claimed methods. The cited patents and published patent applications clearly demonstrate that

the ordinary artisan was aware of heterocyclic carbonyl glycine inhibitors of HIF hydroxylase. Additionally, the specification provides assays for identifying other heterocyclic carbonyl glycine compounds which inhibit HIF hydroxylase for use in the methods as claimed. In sum, the specification provides ample evidence that administration of an effective amount of a heterocyclic carbonyl glycine compound which inhibits HIF hydroxylase will treat diabetes in a diabetic subject, will treat hyperglycemia in a hyperglycemic subject, and will reduce blood glucose levels in a diabetic or hyperglycemia subject. The Examiner has not provided any evidence or reasoning to suggest that this will not occur, and in fact, acknowledges that Applicants have elicited such a response. (See, e.g., Office Action, page 2). Accordingly, the claims are enabled.

Applicants submit that claims 43-56 are enabled. Withdrawal of the rejection of claims 43-56 under 35 U.S.C. §112, 1st paragraph, is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that the claims are fully in condition for allowance and request notification to that effect.

The Commissioner is hereby authorized to charge any fees necessary in this communication to Deposit Account No. 50-0811, referencing Docket No. FP0602.1 US.

Please call Applicants' representative at 415-978-1742 with any questions regarding this communication or the above-identified application.

Respectfully submitted,

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